REMARKS

Entry and consideration of the Amendment is respectfully requested. Claims 11 and 40 have been amended to further clarify the invention. After entry of the Amendment, claims 11, 31, 32, 34, 37 ,38, 40-43, and 58-60 are pending.

The amendment to claims 11 and 40 are supported throughout the specification, including at page 9, lines 9-15 and at page 10, lines 5-6, and does not raise any issues of new matter. Applicants submit the Amendment places the application in condition for allowance and does not raise any issues not previously considered by the Examiner.

Applicants note rejection of the claims under 35 U.S.C. § 102 and § 103 in the previous Office Action (see items 10-13 in Paper No. 9) have been withdrawn by the Examiner.

Claim Objections

The Examiner objected to claim 40 because of a period after (a). Applicants have deleted the period and respectfully request withdrawal of the objections of the claims.

Utility

The Examiner rejected claims 11, 31, 32, 34, 37, 38, 40-43, and 58-60 under 35 U.S.C. § 101 as not supported by either a specific and substantial asserted utility or a well established utility. Applicants respectfully traverse this rejection.

The Examiner maintains the asserted utility of the claimed antibodies is not substantial or specific because the instant specification does not disclose a substantial or specific utility for the polypeptide of SEQ ID NO:1. Applicants respectfully disagree. Applicants submit that the Examiner has not established a prima facie case of lack of utility. Applicants submit that one of skill in the art would find Applicants' asserted utility to more likely than not to be true. Applicants also submit that absolute certainty is not required.

The Examiner asserts Applicants have improperly attempted to apply the teachings of Brenner et al., 1998, *Proc. Natl. Acad. Sci. USA*, 95:6073-6078. Applicants disagree. Brenner et al. assess the performance of different sequence comparison methods for identifying homologs as it would be employed by one skilled in the art attempting to identify homologs of a specific protein. To assess this performance, Brenner et al. used the SCOP database as a sample

population of proteins. The assessment of the performance used proteins that were structurally and functionally characterized. Brenner et al. found that pairwise sequence comparison methods are capable of detecting almost all relationships between proteins whose sequence identities are greater than 30% (Brenner et al., Abstract at page 6073 and figure 3 at page 6075). Brenner et al. also found that pairwise sequence comparison methods utilizing statistical scores, such as E-values, recognized greater than 90% of the homologous pairs with 30-40% identity (Brenner et al. at page 6077). Brenner et al. conclude that E-values give fairly accurate estimates of the significance of pairwise sequence matches and that the homologous proteins found by sequence comparison can be distinguished with high reliability from the huge number of unrelated pairs. (Brenner et al. at pages 6077-6078). The study of Brenner validated the use of sequence comparison methods to establish that % sequence identity comparisons greater than 30% are predictive of shared function.

Applicants' methods for identifying protein sequence homology included statistical scores and dot-matrix homology plots to distinguish regions of significant homology from chance matches (see the specification at page 35). Brenner et al. teach that pairwise sequence comparison methods are capable of detecting almost all relationships between proteins whose sequence identities are greater than 30% (Brenner et al., Abstract at page 6073 and figure 3 at page 6075). Therefore, one skilled in the art would recognize that the teaching of Brenner et al. validates the establishment of the utility of NAPTR based on 48% sequence homology to NPT1.

The Examiner maintains that laboratory experiments are required to verify a protein's function or to know for certain the protein's function and that errors are inherent in predicting function based on sequence identity. Citing Brenner et al., 1999, *Trends Genetics*, 15:132-133, the Examiner asserts 1) that without laboratory experiments it is impossible to know for certain whether the function assigned to a protein by annotation is correct and 2) it is well known in the art that structural identity is not necessarily predictive of functional similarity. (emphasis added) As a specific example, the Examiner cites Scott et al., 1999, *Nat. Genet.*, 21:440-443 which teaches a polypeptide having 45% sequence identity with a human sulfate transporter that functions as a sodium independent transporter of chloride and iodide. Citing Scott et al., the Examiner asserts a skilled artisan would recognize that the function of a polypeptide cannot be assigned based solely on sequence identity, and would conclude that the specification has not

established with a reasonable probability that the polypeptide of SEQ ID NO:1 shares the same function as NPT1 or belongs to the class of phosphate transporters. Applicants respectfully disagree.

Applicants submit that the Examiner is requiring Applicants to establish utility to a higher degree of certainty than is required. Applicants do not have to provide evidence sufficient to establish that an asserted utility is true beyond a reasonable doubt. *In re Irons*, 340 F.2d 974, 978 (CCPA 1965). Nor do Applicants have to provide evidence that establishes the asserted utility as a matter of statistical certainty. *Nelson v. Bowler*, 626 F.2d 853, 856-867 (CCPA 1980). Rather, Applicants only have the burden of presenting evidence that leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. MPEP § 2107.02 (emphasis in original). Applicants submit that the evidence that they have provided establishes that the utility asserted is more likely than not to be true.

First, given the chemical and structural homology between a polypeptide having an amino acid sequence of SEQ ID NO:1 and human renal sodium phosphate transport protein (NPT1; GI 450532), Applicants assert specific utility is based on a known function of NPT1, namely transport of phosphate molecules across cellular membranes. Applicants have provided evidence based on Brenner et al. that sequence identity between polypeptides is a reliable technique in the art for identifying type I phosphate cotransporters. Similar to Applicants, Ishibashi et al. (*Nephron Physiol.*, 94:10-18 (2003); copy enclosed) identified a new member of type 1 Na/phosphate cotransporter in the rat kidney based on sequence homology to the type I Na/phosphate cotransporters. Similar to a polypeptide having an amino acid sequence of SEQ ID NO:1, the polypeptide disclosed in Ishibashi et al. had 44% amino acid sequence identity with human NPT1 (also known as Solute Carrier family 17, member 1) and 30-65% amino acid sequence identity with the other type I class of cotransporters. A polypeptide comprising a sequence of SEQ ID NO:1 has about 70% identity to the rat kidney sequence of Ishibashi et al. (alignment provided). The polypeptide disclosed in Ishibashi et al. mediated phosphate transport across a cellular membrane. Applicants therefore submit that one skilled in the art of phosphate cotransporters would recognize that sequence identity between polypeptides is a reliable technique for identifying Type I phosphate cotransporters and would conclude that the specification has established that it is more likely than not true that the polypeptide of SEQ ID

NO:1 shares the same phosphate transport function as NPT1 or belongs to the Type 1 class of phosphate transporters. Thus, Applicants submit that based on the evidence submitted, one of skill in the art would find Applicants asserted utility to more likely than not to be true.

In addition, the Examiner asserts there must be a well-established or disclosed correlation or relationship between the antibody and a disease or disorder in order for an antibody to be useful. The Examiner maintains the specification merely provides a laundry list of disease that are associated with increased or decreased expression of SEQ ID NO:1 and that there is no indication of what this association may be or how such association may be exploited for disease diagnosis or treatment. Applicants respectfully disagree.

Antibodies to a polypeptide of the amino acid of SEQ ID NO:1 are useful in the purification of a polypeptide of SEQ ID NO:1, and/or diagnosis of disorders associated with an increased or decreased expression of NAPTR. The specification discloses using antibodies to NAPTR in diagnostic assays for disorders associated with decreased or increased expression of NAPTR. Such disorders are indicated at page 22, lines 16-25 of the specification. Antibodies to NAPTR can be utilized in dipstick, pin, ELISA, or chip assays to analyze fluids or tissues from patients to diagnose, for example, a decrease in absorption of phosphate by the kidney or increased phosphate levels in the brain.

The specification also discloses administering antagonists or inhibitors of NAPTR to treat or prevent disorders associated with increased phosphate levels. Examples of disorders associated with increased phosphate levels include hypocalciuria, hypocalcaemia, and abnormal phosphate regulation in neurons, kidney, gastrointestinal tract, and liver. Members of the Type 1 class of phosphate transporters are known to be expressed in liver, kidney, small intestine, and brain. See, for example, the specification at page 10, lines 6-10, and Ishibashi et al. at column 1 on page 11. One skilled in the art of phosphate cotransporters would recognize that sequence identity between polypeptides is a reliable technique for identifying Type I phosphate cotransporters and would conclude that the specification has established with reasonable probability that NAPTR shares the same phosphate transport function as NPT1 or belongs to the Type 1 class of phosphate transporters. An antibody that antagonizes or inhibits phosphate uptake, such as an antibody to NAPTR, could therefore, for example, be exploited to treat

increased phosphate levels in brain or kidney characterized by abnormal phosphate regulation in brain or kidney cells.

Based on the forgoing, Applicants have demonstrated that the specification provides specific and substantial utility for an antibody that specifically binds to a polypeptide comprising an amino acid sequence of SEQ ID NO:1. Applicants have provided evidence that demonstrates it is more likely than not true that a polypeptide comprising the amino acid sequence of SEQ ID NO:1 has specific utility as a transport molecule for phosphate. Antibodies to a polypeptide of the amino acid of SEQ ID NO:1 are useful in the purification of a polypeptide of SEQ ID NO:1, and/or diagnosis of disorders associated with an increased or decreased expression of NAPTR. Antibodies specific for a polypeptide comprising the amino acid sequence of SEQ ID NO:1 that antagonize or inhibit the activity of SEQ ID NO:1 may be exploited to treat, for example, increased phosphate levels in brain or kidney. These utilities are specific to the subject matter claimed and define a real world use.

For at least these reasons, Applicants respectfully request withdrawal of the 35 U.S.C. § 101 rejection.

Enablement

The Examiner rejected claims 11, 31, 32, 34, 37, 38, 40-43, and 58-60 under 35 U.S.C. § 112, first paragraph, as not enabled by the specification. The Examiner contends that one skilled in the art would not know how to use the claimed invention because the claimed invention is not supported by a specific and substantial asserted utility or a well established utility. Applicants respectfully traverse the rejection.

As previously discussed, Applicants assert specific utility for a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 based on chemical and structural homology to NPT1, and the known function of NPT1, namely transport of phosphate molecules across cellular membranes. Applicants have provided evidence that sequence identity between polypeptides is a reliable technique in the art for identifying type I phosphate cotransporters.

Similar to Applicants, Ishibashi et al. identified a new member of type 1 Na/phosphate cotransporter in the rat kidney based on sequence homology to NPT1. Similar to a polypeptide having an amino acid sequence of SEQ ID NO:1, the polypeptide disclosed in Ishibashi et al. had

44% amino acid sequence identity with NPT1 (also known as Solute Carrier family 17, member 1) and 30-65% amino acid sequence identity with another type 1 Na/phosphate transporters. Similar to NPT1, the polypeptide disclosed in Ishibashi et al. mediated phosphate transport across a cellular membrane.

Applicants therefore submit that one skilled in the art of phosphate cotransporters would recognize that sequence identity between polypeptides is a reliable technique for identifying Type I phosphate cotransporters and would conclude that the specification has established with reasonable probability that the polypeptide of SEQ ID NO:1 shares the same phosphate transport function as NPT1 or belongs to the Type 1 class of phosphate transporters.

As previously discussed, the specification provides detailed description and guidance for using the claimed antibodies. Applicants have disclosed several utilities for the antibodies such as use in purification of a polypeptide of SEQ ID NO:1 and diagnostic assays. The specification discloses administering antagonists or inhibitors of NAPTR to treat or prevent disorders associated with increased phosphate levels, including abnormal phosphate regulation in kidney or brain cells. Members of the Type 1 class of phosphate transporters are known to be expressed in liver, kidney, small intestine, and brain. See, for example, the specification at page 10, lines 6-10, and Ishibashi et al. at column 1 on page 11. One skilled in the art of phosphate cotransporters would recognize that sequence identity between polypeptides is a reliable technique for identifying Type I phosphate cotransporters and would conclude that the specification has established with reasonable probability that NAPTR shares the same phosphate transport function as NPT1 or belongs to the Type 1 class of phosphate transporters. As discussed previously, an antibody that antagonizes or inhibits phosphate uptake, such as an antibody to NAPTR, could therefore, for example, be exploited to treat increased phosphate levels in kidney, liver, or brain cells characterized by abnormal phosphate regulation in the cells.

Based on the foregoing, Applicants submit they have enabled the use of the claimed invention. Withdrawal of the rejection is respectfully requested.

The Examiner rejected claims 11, 31, 32, 34, 42, 43, and 58 under 35 U.S.C. § 112, first paragraph, as lacking an enabling disclosure. The Examiner maintains the specification does not reasonably provide enablement for an antibody that binds any polypeptide comprising SEQ ID NO:1. To expedite prosecution of the present application, claim 11 has been amended to recite

an isolated antibody that binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1, wherein the antibody specifically binds to an epitope within the amino acid sequence of SEQ ID NO:1. Applicants, however, do not expressly concede the propriety of the rejection and reserve the right to pursue claims corresponding to the subject matter within the scope of the subject matter of the claims as originally filed in a continuation application.

In view of the amendment to claim 11, withdrawal of the rejection is respectfully requested

Written Description

The Examiner rejected claims 11, 31, 32, 34, 37, 38, 40-43, and 58-60 under 35 U.S.C. § 112, first paragraph, as lacking written description. The Examiner asserts that a genus of polypeptides comprising SEQ ID NO:1 is not fully described in the specification. To expedite prosecution of the present application, claims 11 and 40 has been amended to recite an antibody that binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1, wherein the antibody specifically binds to an epitope within the amino acid sequence of SEQ ID NO:1. Applicants, however, do not expressly concede the propriety of the rejection and reserve the right to pursue claims corresponding to the subject matter within the scope of the subject matter of the claims as originally filed in a continuation application.

In view of the amendment to claims 11 and 40, withdrawal of the rejection is respectfully requested.

Summary

In view of the above amendments and remarks, favorable reconsideration in the form of a Notice of Allowance is respectfully requested. The Examiner is invited to telephone the undersigned for clarification of any of the amendments and remarks or to otherwise facilitate prosecution of the application.

Respectfully submitted,

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